



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :  A61K 9/16, 9/00, 38/28, 38/23, 31/135, 31/485, 38/27, 9/50		A1	(11) International Publication Number: <b>WO 97/35562</b>  (43) International Publication Date: 2 October 1997 (02.10.97)
(21) International Application Number: PCT/GB97/00808		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 24 March 1997 (24.03.97)			
(30) Priority Data:  9606188.2 23 March 1996 (23.03.96) GB			
(71) Applicant ( <i>for all designated States except US</i> ): DANBIOSYST UK LIMITED [GB/GB]; Albert Einstein Centre, Highfields Science Park, Nottingham NG7 2TN (GB).			
(72) Inventors; and		Published.	
(75) Inventors/Applicants ( <i>for US only</i> ): ILLUM, Lisbeth [DK/GB]; 19 Cavendish Crescent North, The Park, Nottingham NG7 1BA (GB). WATTS, Peter, James [GB/GB]; Flat 2, 47 Highfield Road, West Bridgford, Nottingham NG2 6DR (GB).		With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(74) Agent: BASSETT, Richard; Eric Potter Clarkson, St. Mary's Court, St. Mary's Gate, Nottingham NG1 1LE (GB).			

(54) Title: POLYSACCHARIDE MICROSPHERES FOR THE PULMONARY DELIVERY OF DRUGS

## (57) Abstract

There is provided improved compositions for the delivery of pharmacological agents to the respiratory tract of a mammal to provide improved peripheral deposition and systemic uptake wherein a therapeutic agent is incorporated into a polysaccharide microparticle through a process of spray drying.

include the products of biotechnology (in the form of therapeutic proteins (such as granulocyte colony stimulating factor, erythropoietin, interferons and growth hormone)) as well as polypeptide drugs produced by synthesis (such as calcitonins, parathyroid hormone, desmopressin, LHRH analogues (buserelin, 5 goserelin and nafarelin, cholecystokinin and atrial naturetic peptide). Insulin can be considered to be the best known drug which exhibits this problem.

- Other examples of compounds which demonstrate poor absorption from the intestines are polysaccharide materials such as heparin (and its low molecular weight derivatives), antisense agents, polar metabolites of opioid analgesics (morphine-6-glucuronide). Certain other drugs, when given orally, may be absorbed *via* the intestines, but are extensively metabolised in the wall of the intestines or the liver; this is termed "the first pass effect".
- 15 Thus, the skilled person is presented with the problem of the provision of an alternative or a more effective delivery means for use with *inter alia* the abovementioned "challenging" therapeutic agents.

In previous patent applications the applicants have described how molecules 20 including some of those mentioned above may be delivered *via* the nasal and vaginal routes. The applicants have now found that it is possible to deliver such molecules to the lungs for local and systemic treatment by incorporation (i.e. encapsulation) of drug inside a polysaccharide microsphere *via* a novel process, described hereinafter.

25 It is known to those skilled in the art that drugs may be well absorbed *via* the lungs; even polar molecules such as peptides and proteins are quite well absorbed (40% or better appearing in the blood) when delivered to the peripheral airways. The prior art has been reviewed by Niven *et al* 30 Pharmaceutical Research. 13 1242 (1995). In measuring the effectiveness of

the absorption of a drug *via* the pulmonary route, studies are usually conducted *via* animal experiments, which typically install solutions of drugs directly into the lungs. This, of course, is impractical for therapy in man.

- 5 In the delivery of polar drugs to human patients, nebuliser systems are used, in which a mist of drug solution is inhaled into the lungs over an extended period (about 10 - 15 minutes). This is also an effective means of delivering a dose of drug to the lower (peripheral) airways. However, this method of dosing suffers from the disadvantage that it is unpopular with patients because  
10 of the time required to administer drug. Moreover, the process of nebulisation is also known to cause degradation of certain drugs.

There thus exists a need for an effective means for delivering such drugs in a pulsatile or controlled fashion to the lungs. Various devices exist for this  
15 purpose, such as metered dose inhalers (MDIs), which are usually based on a volatile propellant such as a CFC liquid (or a newer, non-CFC, alternative), and dry powder devices.

However, the problem with all such devices is that the quantity of drug  
20 reaching the lungs is quite small (20% or less in many cases). Moreover, the quantity reaching the peripheral airways (for good absorption into the blood) can be less than 10%, and is indeed more often less than 1%. Hence, even though a drug may be well absorbed from the lower (peripheral) regions of the lung, currently available devices are often not able to deliver a sufficient  
25 quantity to this area, in order to produce the desired therapeutic effect. Various attempts are being made to overcome this deposition problem and new devices have been described in the scientific and patent literature. Powder devices are popular in this regard.

- 30 Notwithstanding the mechanical properties of the device, and the spacer system

which may be used with such a device, the problem also exists that the powder system containing the drug needs to have appropriate properties to enable effective deposition.

5 It is well known to those skilled in the art that solid particles intended for delivery to the lungs should be of an aerodynamic diameter (as defined in "Aerosols in Medicine", Morén *et al*, Elsevier (1993), at page 64) of less than 10 microns and, preferably, of less than 5 microns. However, the particles should not be too small, or the particles will fail to deposit in the lung and be  
10 exhaled. A size range of 0.5 to 5 microns is thus preferred. Complex drugs such as peptides and proteins, low molecular weight heparin, antisense agents, DNA, may be micronised in order to produce this size range, but this process is known to cause damage to labile molecules. Moreover, physical losses can occur during the active processing operation.

15

In addition, many of the products of biotechnology, in the form of peptides and proteins, must be administered in very low doses (e.g. less than 1 mg). The pharmaceutical formulation can therefore suffer from problems of dose size and dose uniformity. Such drugs may be mixed *via* an appropriate means with an  
20 inert carrier, and lactose and mannitol are often used for this purpose (see, for example, WO 95/31479). However, problems associated with dose uniformity and segregation of the active material may still be exhibited. Furthermore, certain drugs are known to be surface active, or have properties than can greatly affect the electrostatic and flow properties of simple mixed systems.

25

In summary therefore, in view of the inadequate nature of currently available powder systems, and the poor performance of such systems in powder devices, a major problem exists in relation to the effective delivery of the abovementioned "challenging" drugs to the lung by way of powder systems.  
30 We have surprisingly found that microspheres prepared from soluble

polysaccharides prepared by way of a spray drying process can overcome these problems.

- Microspheres for administration to the lung have also been reviewed by Zeng *et al* (see International Journal of Pharmaceutics, 107, 205 (1994) and 124, 149 (1995)). Albumin microspheres for lung delivery have also been described in CA 2036844 and by Zeng *et al* (International Journal of Pharmaceutics, 109, 135 (1994)). In these documents, microspheres are prepared by a conventional method involving emulsification and cross-linking. Solid microspheres, prepared by such a cross-linking process, are expected to have unsatisfactory degradation properties in the lung. Moreover, the cross-linking of the carrier in the manner described in this prior art in the presence of a sensitive drug, such as a peptide or protein, is also expected to cause chemical modification of that drug. The preparation of cross-linked microspheres of polysaccharides for controlled release by emulsifying vinyl derivatives of hydrophilic polymers is described in EP 245820 and by Artursson *et al* (J. Pharm. Sci. 73, 1507 (1984)). Questions can be raised concerning biodegradation and safety for reasons including those discussed below.
- Starch microspheres cross-linked with epichlorohydrin produced *via* an emulsification process have been reported for the nasal administration of drugs. Whilst the majority of the microspheres can be degraded (for example by amylases), a small amount of cross-linked material, when produced in this way always remains in the nasal cavity. Whilst this is of no concern in nasal delivery, it is expected to lead to adverse effects in the lung, especially if the particles were delivered to the alveolar regions where they would not be cleared by the mucociliary clearance process.
- The administration of lactide/glycolide copolymer nanospheres for pulmonary delivery of peptide drugs such as LHRH analogues has been reported by Niwa

*et al* (Yakugaku Zasshi, Journal of the Pharmaceutical Society of Japan, 115, 732, (1995)). The particles were prepared by an emulsification process.

In a previous patent application (WO 93/02712) the applicants have described  
5 how hollow and solid microspheres can be prepared using a double  
emulsification process from soluble starch. It was suggested that such particles  
could be useful for the delivery of drugs to the lung. Microporous spherical  
particles have been described in US 4818542. The agents mentioned here  
included starch. A pore incorporating agent was also included in the  
10 formulation process.

Spray dried microparticles have been described in the prior art. Spray dried  
soluble proteins are described in EP 315875, WO 92/18164, WO 94/08627.  
In WO 94/08627, wall forming materials for hollow microcapsules included  
15 polysaccharides of low solubility. The use of such microspheres for delivery  
to the lung was not disclosed. Spray drying of pregelatinized starch and of  
pregelatinized hydroxypropyl starch is described in US 4871398 and US  
4847371 respectively. In neither case is the use of spray drying of soluble  
polysaccharides for the preparation of drug loaded particles for pulmonary  
20 administration described. In EP 611567, sustained-release microparticles for  
pulmonary delivery are produced by spray drying a drug in the presence of  
hydroxypropyl cellulose and/or hydroxypropyl methyl cellulose; the formation  
of microspheres is not mentioned.

25 **Detailed Description of the Invention**

We have found surprisingly that, by using soluble polysaccharides, such as  
starches, and a spray drying process, in which drug is mixed in solution with  
the polysaccharide material prior to spraying, it is possible to produce, in one  
30 step, microspheres in which drug is incorporated (i.e. encapsulated), that have

the preferred size range for good lung deposition.

- According to the invention there is thus provided a composition for the delivery of pharmacological agents to the respiratory tract of a mammal, to provide
- 5 improved peripheral deposition and systemic uptake, wherein the therapeutic agent is incorporated into a polysaccharide through a process of spray drying, which compositions are hereinafter referred to together as "the compositions according to the invention".
- 10 The compositions according to the invention are characterised by virtue of the fact that they are microspheres. The term "microspheres" will be well understood by those skilled in the art. The term thus includes those microparticles of a substantially spherical nature, and excludes those of a substantially granular and/or non-spherical nature, which latter particles may
- 15 be made by mixing pharmaceutical agents with carriers or bulking agents by a suitable process, followed, if necessary, by further processing (e.g. pulverizing, micronising) to form a powder. In these contexts, by "substantially" we mean greater than 80%, preferably greater than 90%, spherical, granular and non-spherical, respectively.
- 20
- The term polysaccharide will be well understood by those skilled in the art to exclude disaccharides, such as lactose. The compositions according to the invention comprise polysaccharides which have a molecular weight between 10,000 and 1,000,000, preferably between 50,000 and 75,000 and particularly
- 25 between 100,000 and 300,000, and which are soluble in water. By "soluble in water" we mean that a solution of the polysaccharide can be prepared in aqueous solution at a concentration of 1 mg/ml or greater.

30 The compositions according to the invention have excellent flow properties and have the considerable advantage that they exhibit good (i.e. high) and uniform

- loading of drugs. Although the compositions according to the invention permit loadings of drug as high as 50%, by "high loading of drugs" we mean a drug loading of greater than 10%. Furthermore, the compositions according to the invention have an improved performance *in vivo*, as determined in studies using  
5 human volunteers. When administered in a powder device, the compositions according to the invention exhibit superior properties when compared to a formulation prepared by the micronization of the drug to a size suitable for administration to the lung and its admixture with the carrier material lactose.
- 10 Microspheres may be formed in one step by spray drying a mixture of drug and soluble polysaccharide in solution.
- According to a further aspect of the invention there is provided a method for preparing microspheres for the improved delivery of pharmacological agents to  
15 the respiratory tract of a mammal wherein the said agent is incorporated into a microsphere using a one step process where the drug is mixed in solution with a soluble polysaccharide and thereafter particles formed through a process of spray drying, which method is hereinafter referred to as "the process according to the invention".  
20 The microspheres prepared by the process according to the invention also possess considerable advantages when compared to microspheres formed from polysaccharides as described in the prior art, by virtue of the fact that they may be prepared by a one step process. The microspheres prepared by the process  
25 according to the invention also have the advantage that they can be collected as a product that can be used without further processing. Moreover, the particle size distribution is narrow.

30 The compositions according to the invention may be prepared by spray drying aqueous solutions of polysaccharide, or polysaccharide in an emulsion system.

When an emulsion system is used, microspheres can be prepared by spray drying polysaccharide in single (w/o) or (o/w) or double (w/o/w) (o/w/o) emulsion systems, the oil phase consisting of a volatile water immiscible solvent such as chloroform, methylene chloride and/or perfluorocarbons. In the 5 emulsion systems the drug can either be dissolved in the water phase (hydrophilic drugs) or the oil phase (lipophilic drug).

However, a preferred method of producing drug loaded microspheres is as follows:

10

The drug is dissolved in water to produce a concentrated solution. The amount of drug employed will depend on the dose of drug that will be required in the final dose of the microsphere formulation and may vary from 0.1 mg to 2 g, more typically 1 g, of drug dissolved in 10 ml of distilled water.

15

The soluble polysaccharide is also dissolved in distilled water. The quantity of polysaccharide used will depend on its gelation and rheological properties, and can be varied from 0.1 g to 20 g in 200 ml, though typically 1 gram of polysaccharide will be dissolved in 20 ml of distilled water. For charged 20 polysaccharides the pH and ionic strength of the solution can be adjusted by an appropriate means (such as those described hereinafter), but with clear recognition of the fact that the resultant microspheres will be delivered into the lung and that excessive quantities of electrolyte could alter the swelling and drug release properties of the final product.

25

The drug and polysaccharide solutions may then be combined. Preferred concentrations of polysaccharide in the combined solution are between 0.5 and 5 g per 20 ml and especially preferred concentrations are in the range 0.75 - 3 g per 20 ml. The viscosity of the resultant drug/polysaccharide solution 30 should be suitable for dispersion in the selected spray drying device. A

solution viscosity in the range 1 - 15 centipoise is preferred. For a non-Newtonian system such viscosity is measured as an apparent viscosity at a shear rate of 100 sec<sup>-1</sup>.

- 5    The drug/polysaccharide solution can then be dispersed into microspheres using a suitable spray drying apparatus. Suitable apparatuses include that described hereinafter in the examples (i.e. the LabPlant SD-05 equipment available from LabPlant, Huddersfield, UK). Other suitable equipment which may be employed include the apparatus available from Buchi in Switzerland. The  
10   operating conditions such as the flow rate of the solution into the spray dryer, the size of the nozzle, the inlet and outlet air temperature, the atomization pressure and the flow rate of the drying air can be adjusted in accordance with the appropriate manufacturer's guidelines in order to provide the required particle size and release properties for the resultant microspheres. Such  
15   optimization conditions can be easily selected by the person skilled in the art of pharmaceutical formulation paying proper attention to known methods of experimental design. However, when the LabPlant SD-05 is used, preferred conditions are as follows: an inlet air temperature of between 100 and 200°C; an outlet air temperature of between 50 and 100°C; and spray rate of between  
20   1 and 20 ml/min; a drying air flow of between 8 and 28 m<sup>3</sup>/h; an atomizing pressure of between 1 and 4 bar; and a nozzle size of between 0.1 and 2 mm. By using such methods, particles with a size appropriate for deposition in the different regions of the lung (i.e. an aerodynamic diameter of less than 10 microns, see above) and a narrow size distribution can be achieved.

25

- The abovementioned spray drying process may, of course, also be used to prepare microspheres from polysaccharides in an emulsion system. However, when the preferred non-emulsion process is used, the compositions according to the invention have the additional advantage that they are not contaminated  
30   with solvents or oils used, as is the case in methods based on emulsification.

The compositions according to the invention can be administered to the lung in quantities from 1 - 100 mg of microspheres using an appropriate powder device. A preferred quantity of microspheres is in the range 5 - 50 mg. The drug content of the microsphere may range from a loading of less than 1% w/w of the microsphere to more than 50% w/w loading. The level of loading will, of course, be dictated by the therapeutic activity of the drug, the quantity of microspheres that can be delivered to the lung by the selected device, and the effect of the drug on the physical properties of the microsphere. Typically, loading will be between 1 and 10% w/w of drug to microsphere.

10

According to a further aspect of the invention, there is thus provided a method for the improved systemic delivery of pharmacological agents to a mammal by the respiratory tract, which comprises administering a composition according to the invention to a patient.

15

The compositions according to the invention have been found to gel and dissolve in the lung and are entirely biocompatible. In particular, when compositions according to the invention are prepared, which do not include the crosslinking agent or starch gel modifiers mentioned below, they are characterised by virtue of the fact that they may be dissolved rapidly (e.g. in less than five minutes, usually less than two minutes) and completely (e.g. a solution is formed at a concentration of 1 mg/ml or greater), when placed in water.

20  
25 The compositions according to the invention may be prepared using different soluble polysaccharides. These include, but are not limited, to amyloextrin, amylopectin, hydroxyethylstarch, carboxymethylcellulose, diethylaminoethyl-dextran, dextran, pullulan, carboxymethyl pullulan or polyglucosamine. We also include mucopolysaccharides such as hyaluronic acid in this definition.

30

We prefer that the polysaccharide is not a cellulose alkyl ether such as hydroxypropyl cellulose or hydroxypropyl methyl cellulose. Preferred polysaccharides include hydroxyethylstarch.

- 5 We have also found that, by varying the concentration of the soluble polysaccharide, and using different processing conditions, such as degree of crosslinking or addition of starch gel modifiers, it is possible to provide particles with different sizes and different release characteristics. Thus, in this manner, the drug can be released rapidly (for example to provide early  
10 appearance in the blood) or slowly (for example if the drug is required for local effects in the lung tissue or lung microcirculation).

By "released rapidly" we mean immediate release following delivery to the lung, which includes release of more than 50%, preferably more than 70%, and  
15 more preferably more than 80%, of drug just after (i.e. up to 5 minutes after) delivery to the lung. By "released slowly" we mean controlled release over a period of up to 6 hours following delivery to the lung.

- However, we prefer that drug is released rapidly to the lung following delivery.  
20  
It is thus feasible to mix the polysaccharide solution with other excipients such as to provide a controlled release of the drug. Examples of such excipients are phospholipids, cyclodextrins, gelatin, alginate. Cross-linking agents may also be used to provide a controlled release of drug but, when this is the case it/they  
25 is/are chosen from material(s) that will provide total biodegradation of the microparticles. Polyphosphates are particularly preferred for this purpose for use with polysaccharides. Alternatively, aldose sugars can be used for polyglucosamines. Appropriate starch gel modifiers for use in the compositions according to the invention include fatty acids, preferably sodium myristate and monoglycerides.  
30

In the compositions according to the invention, more than 80%, and preferably more than 90%, of microspheres have an aerodynamic diameter, or a particle size, of between 0.1 to 10  $\mu\text{m}$ , more preferably between 0.5 to 5  $\mu\text{m}$ , as measured by a Malvern Mastersizer or by optical microscopy.

5

The novel microspheres can, depending upon the preparation method, be loaded with lipophilic drugs or more especially, water soluble drugs. By "water soluble drugs" we mean that a solution of the drug can be prepared in the solution of soluble polysaccharide at a concentration of 1 mg/ml or greater.

10 Examples include insulin, calcitonin, parathyroid hormone, cholecystokinin, desmopressin, leutinizing hormone releasing hormone and analogues thereof, human growth hormone, growth hormone releasing hormone, interferon (alpha, beta, consensus), leptin, somatostatin, superoxide dismutase, erythropoietin, colony stimulating factors, oligonucleotides, heparin, or a low molecular weight derivative thereof (by "low molecular weight" we mean a molecular weight of less than 10,000), DNA, analgesics (including polar analgesics such as morphine and metabolites thereof (including polar metabolites such as the glucuronides of morphine)). By "polar" we mean a molecule with partition coefficient (octanol-water system) of less than 100. Other drugs and the salts

15 of drugs which can be used include drugs for asthma treatment, immunomodulators, nicotine salts, soluble salts of salbutamol, terbutaline, and sodium cromoglycate. Antihistamines such as azatadine maleate, diphenhydramine hydrochloride, cardiovascular drugs such as diltiazem hydrochloride, timolol maleate, analgesic agents such as pethidine

20 hydrochloride, hydromorphone hydrochloride, propoxyphene hydrochloride and tranquilisers such as promazine hydrochloride may also be used. Other examples of active pharmacological ingredients of high solubility in water are listed in US 5202128 and are included herein by reference.

25 30 Proteins for local treatment, which can also be incorporated into the

microspheres include monoclonal and polyclonal antibodies, alpha 1 - antitrypsin, deoxyribonuclease. The protein drugs described above can also be administered as their chemical conjugates with polyethylene glycol.

- 5 Combinations of any of the abovementioned drugs may also be used.

- The microsphere powders produced in the present invention may be used in a suitable dry powder device familiar to those skilled in the art. These include, but are not limited to, the Spinhaler™ (Fisons plc), Lyphodose™ (Valois S.A.),  
10 Monopoudre™ (Valois S.A.), Valois DPI™ (Valois S.A.), Turbospin™ (Phildeatech), multichamber powder inhaler (Pfeiffer), Turbohaler™ (Astra-Draco AB), Rotahaler™ (Glaxo), Diskhaler™ (Glaxo), Pulvinal™ (Chiesi Farmaceutici SpA) and Ultrahaler™ (Fisons).
- 15 Additionally, the microspheres may be lightly compacted to produce a solid compact from which a dose is taken via a mechanical method (eg. Ultrahaler™, Fisons). If necessary the microspheres can also be mixed with a small amount of excipients such as lactose to improve flow properties.
- 20 The invention is illustrated, but in no way limited, by way of the following examples.

#### Brief Description of the Figures

- 25 Figure 1 shows an emitted dose plot for micronised insulin, dispensed from a Fisons Ultrahaler™, as determined using an Emitted Dose Apparatus (Multi-stage Liquid Impinger (MSLI)) in which the amount of dose to the MSLI, and the dose to patient (DTP: calculated from the MSLI), are plotted against dose number/device number.

Figure 2 shows an emitted dose plot for an insulin microsphere formulation, dispensed from a Fisons Ultrahaler™, as determined using an Emited Dose Apparatus (Multi-stage Liquid Impinger (MSLI)) in which the amount of dose to the MSLI, and the dose to patient (DTP; calculated from the MSLI), are plotted against dose number/device number.

### Example 1

#### Preparation of 50:50 (w/w) insulin:starch microspheres

10 1 g of soluble potato starch, (Sigma, Poole, UK) was dissolved in 20 ml of distilled water. The starch was dissolved by heating the mixture to 90°C, with continuous mechanical stirring, then allowed to cool to 30°C without assistance.

15 1 g of zinc insulin (Novo-Nordisk, Denmark) was dissolved in 10 ml of 0.1 N HCl, with continuous mechanical stirring. The pH of the solution was then adjusted to pH 7.2 by dropwise addition of 0.1 N NaOH.

20 The starch solution and insulin solutions were combined and mechanically stirred for ten minutes. The pH of this solution was 7.1. The solution was spray-dried using a LabPlant SD-05 spray dryer (LabPlant, Huddersfield, UK) with the following process conditions: solution flow rate 5 ml/min, atomising nozzle diameter 0.5 mm, inlet air temperature 120°C, outlet air temperature 70°C, drying airflow 50% setting.

25

The collected microspheres were examined by light microscopy. The particles were spherical and had a particle size in the range 3-8 µm.

**Example 2****Preparation of 1.18% w/w calcitonin:hydroxyethyl starch (HES) microspheres**

- 5 0.5 g of HES (Mw 200000; Fresenius, Austria) was dissolved in 20 ml of distilled water. 0.006 g of salmon calcitonin (sCT; Peptech) was dissolved in 10 ml of distilled water.

10 The HES and sCT solutions were combined and mixed. The solution was spray-dried using a LabPlant SD-05 spray drier (LabPlant, Huddersfield, UK) using the following process conditions: solution flow rate 8 ml/min, atomising nozzle diameter 0.5 mm, inlet air temperature 155°C, outlet air temperature 79-81°C, drying airflow 19 m<sup>3</sup>/h, atomising air pressure 1.9 bar.

- 15 The collected microspheres were examined by optical and scanning electron microscopy. Spherical particles with a particle size in the range 2-5 µm were observed.

**Example 3****Preparation of 20% w/w insulin:HES microspheres**

- 16.212 g of HES (Mw 200000; Fresenius, Austria) was dissolved in 250 ml of distilled water. 3.788 g of zinc insulin (Lilly) was dissolved in 50 ml of 0.1 N HCl with continuous mechanical stirring. The pH of the solution was then 25 adjusted to pH 7.2 by dropwise addition of 0.1 N NaOH.

The HES and insulin solutions were combined and made up to a final volume of 600 ml. The solution was spray-dried using a LabPlant SD-05 spray drier (LabPlant, Huddersfield, UK) using the following process conditions. Solution flow rate 8 ml/min, atomising nozzle diameter 0.5 mm, inlet air temperature 30

175°C, outlet air temperature 75-85°C, drying airflow 19 m<sup>3</sup>/h, atomising air pressure 1.9 bar.

- The collected microspheres were examined by optical microscopy. Spherical  
5 particles with a particle size in the range 2-5 µm were observed.

#### Example 4

##### Preparation of 5% w/w terbutaline:HES microspheres

- 10 A HES stock solution was prepared by dissolving 25.0 g of HES in 200 ml of ultrapure water. A terbutaline stock solution was prepared by dissolving 1250 mg of terbutaline sulphate in 200 ml of ultrapure water.

- 200 ml of each of the stock solutions were then made up to 500 ml with  
15 ultrapure water. The solution was spray-dried using a LabPlant SD-05 Spray Drier (LabPlant, Huddersfield, UK) using the following process conditions:

	Inlet air temperature:	175°C
	Outlet air temperature:	75 - 85°C
20	Pump speed:	4 - 5
	Airflow:	20 units
	Atomizing pressure:	1.9 bar
	Nozzle size:	0.5 mm

- 25 The microspheres were collected and had a spherical appearance. The yield was 40%.

**Example 5****Preparation of 50% w/w morphine:HES microspheres**

5 A HES stock solution was prepared by dissolving 2.0 g of HES in 200 ml of ultrapure water. A morphine stock solution was prepared by dissolving 2667 mg of morphine sulphate (equivalent to 2000 mg morphine base) in 200 ml of ultrapure water.

10 200 ml of each of the stock solutions were then made up to 500 ml with ultrapure water. The solution was spray-dried using a LabPlant SD-05 Spray Drier (LabPlant, Huddersfield, UK) using the following process conditions:

Inlet air temperature:	175°C
Outlet air temperature:	75 - 85°C
15 Pump speed:	4 - 5
Airflow:	20 units
Atomizing pressure:	1.9 bar
Nozzle size:	0.5 mm

20 The microspheres were collected and had a spherical appearance. The yield was 18%.

**Example 6****Preparation of 10% w/w human growth hormone:carboxymethyl cellulose microspheres**

25 A carboxymethyl cellulose stock solution was prepared by dissolving 900 mg of carboxymethyl cellulose in 25 ml of ultrapure water. A human growth hormone (hGH) stock solution was prepared by dissolving 100 mg of hGH in 30 25 ml of ultrapure water.

25 ml of each of the stock solutions were then made up to 100 ml with ultrapure water. The solution was spray-dried using a LabPlant SD-05 Spray Drier (LabPlant, Huddersfield, UK) using the following process conditions:

5	Inlet air temperature:	175°C
	Outlet air temperature:	75 - 85°C
	Pump speed:	4 - 5
	Airflow:	20 units
	Atomizing pressure:	1.9 bar
10	Nozzle size:	0.5 mm

The microspheres were collected and had a spherical appearance. The yield was 42%.

15 **Example 7**

***In vitro* characterisation of insulin:HES microspheres delivered from a Dry Powder Device**

20 The aerodynamic properties of the microspheres from Example 3 above were characterised *in vitro* using an Astra-type four stage liquid impinger (Copley Instruments, Nottingham, UK). The instrument was operated at a flowrate of 60 l/min using water as the collection fluid. 150 mg of insulin:HES microspheres were loaded into the reservoir of a powder aerosol device (Valois Prohaler). The firing chamber was primed and ten shots were fired into the 25 impinger. Each shot delivered approximately 5 mg of microspheres. The distribution of the collected material in the impinger is shown in Table 1.

**Table 1.**

**Distribution of insulin microsphere formulation in an impinger, fired from a dry powder device.**

5	Size of cut off (micron)	% Insulin	
		Run 1	Run 2
	Throat	11.5	21.6
	> 6.8	19.0	20.2
	< 6.8	69.5	58.2

- 10 The high percentage of respirable particles below 6.8 microns is notable.

### **Example 8**

***In vitro* characterisation of 5% w/w terbutaline:HES microspheres delivered from a Dry Powder Device**

15

The microspheres from Example 4 above were loaded into preweighed dosing chambers of a Valois Prohaler System and the aerodynamic properties of the microspheres were characterised *in vitro* using an Astra-Draco Multistage Impinger (Copley Instruments, Nottingham, UK). The instrument was operated at a flowrate of 60 l/min using water as the collection fluid. The firing chamber was primed and ten shots were fired into the impinger. Each shot delivered approximately 2.5 mg of microspheres. The drug content at each stage was measured by HPLC. The distribution of the collected material in the impinger is shown in Table 2.

25

Table 2

Distribution of terbutaline microsphere formulation in an impinger, fired from a dry powder device.

5

Size of cut off (micron)	% terbutaline sulphate
Throat	29.6
> 6.8	16.6
< 6.8	54.1

10. The high percentage of respirable particles below 6.8 microns is notable.

#### Example 9

*In vitro characterisation of 50% w/w morphine:HES microspheres delivered from a Dry Powder Device*

15

The microspheres from Example 5 above were loaded into preweighed dosing chambers of a Valois Prohaler System and the aerodynamic properties of the microspheres were characterised *in vitro* using an Astra-Draco Multistage Impinger (Copley instruments, Nottingham, UK). The instrument was operated at a flowrate of 60 l/min using water as the collection fluid. The firing chamber was primed and ten shots were fired into the impinger. Each shot delivered approximately 1.6 mg of microspheres. The drug content at each stage was measured by HPLC. The distribution of the collected material in the impinger is shown in Table 3.

25

**Table 3**

**Distribution of morphine microsphere formulation in an impinger, fired from a dry powder device.**

Size of cut off (micron)	% morphine sulphate
Throat	33.7
> 6.8	21.3
< 6.8	45.1

- 10 The high percentage of respirable particles below 6.8 microns is notable.

#### **Example 10**

#### *In vivo characterisation of microspheres delivered from a Dry Powder Device*

15

The insulin loaded particles prepared in Example 3 and characterised in Example 7 were evaluated in man. Doses of the insulin:HES microspheres were administered to eight healthy volunteers using a dry powder device. Both formulations were radiolabelled by surface adsorption of technetium-99m onto the insulin microspheres. The correspondence between radiolabel and insulin distribution was confirmed *in vitro* using the impinger device described in Example 7. The distribution of the formulations *in vivo* was determined by gamma scintigraphy. The results are shown in Table 4.

**Table 4****Deposition of formulation *in vivo***

Region	% of total activity in body ± standard deviation
Mouth and stomach	$48.4 \pm 8.0$
Trachea	$7.9 \pm 2.7$
Central Lung	$21.1 \pm 7.0$
Peripheral Lung	$19.6 \pm 5.0$

5

Mean  $\pm$  standard deviation ( $n=8$ ). The percentage of the dose reaching the lung was 43.7%.

10

The absorption of insulin was assessed by measuring the change in plasma glucose concentration with time following dosing using a standard method. The results are shown in Table 5.

**Table 5**

**Absorption of insulin in man (n=8) as indicated by the reduction in plasma glucose level**

	Time (mins)	Mean plasma glucose (% basal level)
5	5	83.7
	10	85.5
	20	80.6
	30	77.8
	45	71.5
10	60	77.5
	90	87.6
	120	84.5
	150	87.6
	180	86.3
15	240	91.1

The fact that a rapid reduction in plasma glucose to a value of 72% of the basal level is obtained in 45 minutes is notable.

#### 20    Example 11

*In vitro comparison of micronised insulin and insulin microspheres delivered from a dry powder device*

25    The aerodynamic properties of the microspheres from Example 3 above were characterised *in vitro* as before using an Astra-type four stage liquid impinger (Copley Instruments, Nottingham, UK). The impinger was operated at a flow rate of 60 l/min using water as the collection fluid.

5 mg of insulin:HES microspheres were loaded into the firing chamber of a dry

powder device. The dose was then fired into the impinger. This was repeated to give a total of ten doses in insulin:HES microspheres.

For comparison, a blend of micronised insulin (size range 2-5  $\mu\text{m}$ ) (Lilly, Indianapolis, USA) and anhydrous lactose (45-150  $\mu\text{m}$ ) was prepared. This contained 10% w/w insulin. 10 mg aliquots of this blend were loaded into the firing chamber of the same dry powder device and the test conducted as described above.

10 The distribution of the collected material in the impinger is shown in Table 6.

**Table 6**

**Distribution of insulin:HES microspheres and insulin:lactose powder blend formulations in the 4 stage impinger when fired from a dry powder device**

15 Size of cut off (micron)	Insulin micronised		Insulin in microspheres	
	Run 1	Run 2	Run 1	Run 2
Throat	43.2	12.7	14.4	12.7
> 6.8	29.2	47.4	15.8	16.8
< 6.8	27.6	39.9	69.8	70.6

The fine particle fraction, defined as the amount greater than 6.8 microns, is substantially higher for the microsphere formulation as compared to the simple blend of micronised insulin and lactose.

### **Example 12**

#### ***In vivo* comparison of micronised insulin and insulin microspheres**

Doses of both the insulin:HES microspheres and the powder blend as

characterised in Example 11 were administered to 4 healthy volunteers using a dry powder device.

The absorption of insulin was assessed by measuring the change in plasma 5 glucose concentration with time following dosing using standard methods to measure plasma glucose levels. The results are shown in Table 7.

**Table 7**

**Absorption of insulin in man (n=4) as indicated by the reduction in plasma 10 glucose level**

Time (mins)	Microsphere formulation	Micronised insulin formulation
5	92.0	91.5
10	90.3	87.3
20	89.3	98.0
30	87.3	99.8
45	80.0	93.5
60	80.8	89.3
90	86.2	80.3
120	91.5	84.5
150	93.5	87.5
180	94.5	90.0
240	98.9	93.0

25 It will be seen that, as in Example 10, the insulin when delivered in the starch microsphere system provides an earlier reduction in plasma glucose (time - minimum 45 mins) than the single formulation where the micronised insulin is mixed with lactose before administration (time - minimum 90 mins).

**Example 13*****In vitro comparison of micronised insulin and insulin microspheres delivered from a Fisons Ultrahaler™ dry powder device***

- 5 The Ultrahaler was loaded with either insulin microspheres mixed with lactose or micronized insulin mixed with lactose. The two blends were prepared in the following way: 12.96 g of 50:50 insulin microspheres, prepared as in Example 3, or 6.56 g of micronized insulin (Lilly, Indianapolis, USA) were mixed with 54.0 g of anhydrous lactose in a Turbula T2C mixer set at speed 2 for 5  
10 minutes, after which the powders were sieved through a 355 µm sieve before being remixed for a further 5 minutes in the Turbula mixer.

The two blends were packed into Ultrahaler™ devices and the formulations were evaluated for emitted weight uniformity, emitted dose, and distribution, in an  
15 Astra Draco Multistage Liquid Impinger.

***Emitted Weight Uniformity:*** The evaluation was carried out on three devices using an Emitted Weight Apparatus. A Labweigh computer programme was used to electronically capture the data. The flow rate was set at 60 l/min. For  
20 every dose the Ultrahaler™ was held in the Apparatus for 4 seconds. The filter paper was changed every five doses. The emitted mean weights for the two formulations were 18.75 mg and 14.45 mg for the micronized insulin and the insulin microsphere formulations respectively, with comparable standard deviations. This is consistent with the powder densities.

25

***Emitted Dose:*** The evaluation was carried out on three devices using an Emitted Dose Apparatus. Single shot emitted dose studies were carried out. The doses were individually dispensed into the emitted dose collection apparatus. The flow rate was set at 60 l/min. The device was held in the  
30 apparatus for 4 seconds to allow 4 litres of air to flow through the device.

Each tube was washed several times with the same 20 ml of water. A sample was analysed for insulin content by HPLC. The results are shown in Figure 1 and Figure 2. It can be seen that the microsphere formulation clearly improved the uniformity of the emitted dose as compared to the micronized insulin formulation.

**Multistage Impinger Studies:** The aerodynamic properties of the micronized insulin and insulin microsphere formulations were characterised and compared *in vitro* by firing into an Astra-Draco Multistage Liquid Impinger (Copley Instruments, Nottingham, UK). The instrument was operated at a flow rate 60 l/min using water as the collection fluid. The firing chamber of the powder device was primed and two shots fired into the impinger. The drug content at each stage was determined by HPLC. The results are shown in Table 8.

15 **Table 8**

**Distribution of micronized insulin:lactose and insulin microsphere:lactose formulations in the four stage impinger when fired from the Ultrahaler™ dry powder device.**

20 Size of cut off (micron)	Micronised insulin formulation (% insulin)			Insulin microsphere formulation (% insulin)		
	Device 1	Device 2	Device 3	Device 1	Device 2	Device 3
Throat	37.7	24.7	19.2	24.3	18.7	18.9
> 6.8	32.3	41.4	44.0	30.3	38.8	31.9
< 6.8	30.1	33.9	36.8	45.4	42.5	49.2

25

The improved percentage of respirable particles below 6.8 µm for the microsphere formulation as compared to the micronized insulin formulation is notable.

**CLAIMS**

1. A composition for the delivery of pharmacological agents to the respiratory tract of a mammal to provide improved peripheral deposition and  
5 systemic uptake wherein the therapeutic agent is incorporated into a polysaccharide through a process of spray drying.
- 10 2. A composition as described in Claim 1 wherein the pharmacological agent is a polypeptide or protein intended for local or systemic treatment.
- 15 3. A composition as described in Claim 1 wherein the pharmacological agent is insulin, calcitonin, parathyroid hormone, a leutinising hormone releasing hormone, or analogue thereof, an interferon, desmopressin, superoxide dismutase, leptin, erythropoietin, somatostatin, colony stimulating factor (G-CSF, GM-CSF), cholecystokinin or growth hormone.
- 20 4. A composition as described in Claim 3 wherein the pharmacological agent is insulin or calcitonin.
- 25 5. A composition as described in Claim 4 wherein the pharmacological agent is insulin.
6. A composition as described in Claim 1 wherein the pharmacological agent is a low molecular weight heparin.
- 25 7. A composition as described in Claim 1 wherein the pharmacological agent is an oligonucleotide or DNA.
- 30 8. A composition as described in Claim 1 wherein the pharmacological agent is a polar analgesic agent, or a polar metabolite thereof.

9. A composition as described in Claim 8 wherein the polar analgesic agent is morphine.
10. A composition as described in Claim 8 wherein the polar metabolite is 5 morphine-6-glucuronide.
11. A composition as described in any one of Claims 1 to 10 wherein the polysaccharide material is soluble starch or amylodextrin.
- 10 12. A composition as described in any one of Claims 1 to 10 wherein the polysaccharide material is hydroxyethyl starch.
13. A composition as described in any one of Claims 1 to 10 wherein the polysaccharide is polyglucosamine.
- 15 14. A composition as described in any one of Claims 1 to 10 wherein the polysaccharide is amylopectin or amylose.
16. A composition as described in any one of Claims 1 to 10 wherein the polysaccharide is dextran or pullulan.
- 20 17. A composition as described in any one of Claims 1 to 10 wherein the polysaccharide is carboxymethyl cellulose or carboxymethyl pullulan.
- 25 18. A composition as described in any one of Claims 1 to 17 wherein the particles are between 0.1 and 10 microns in size.

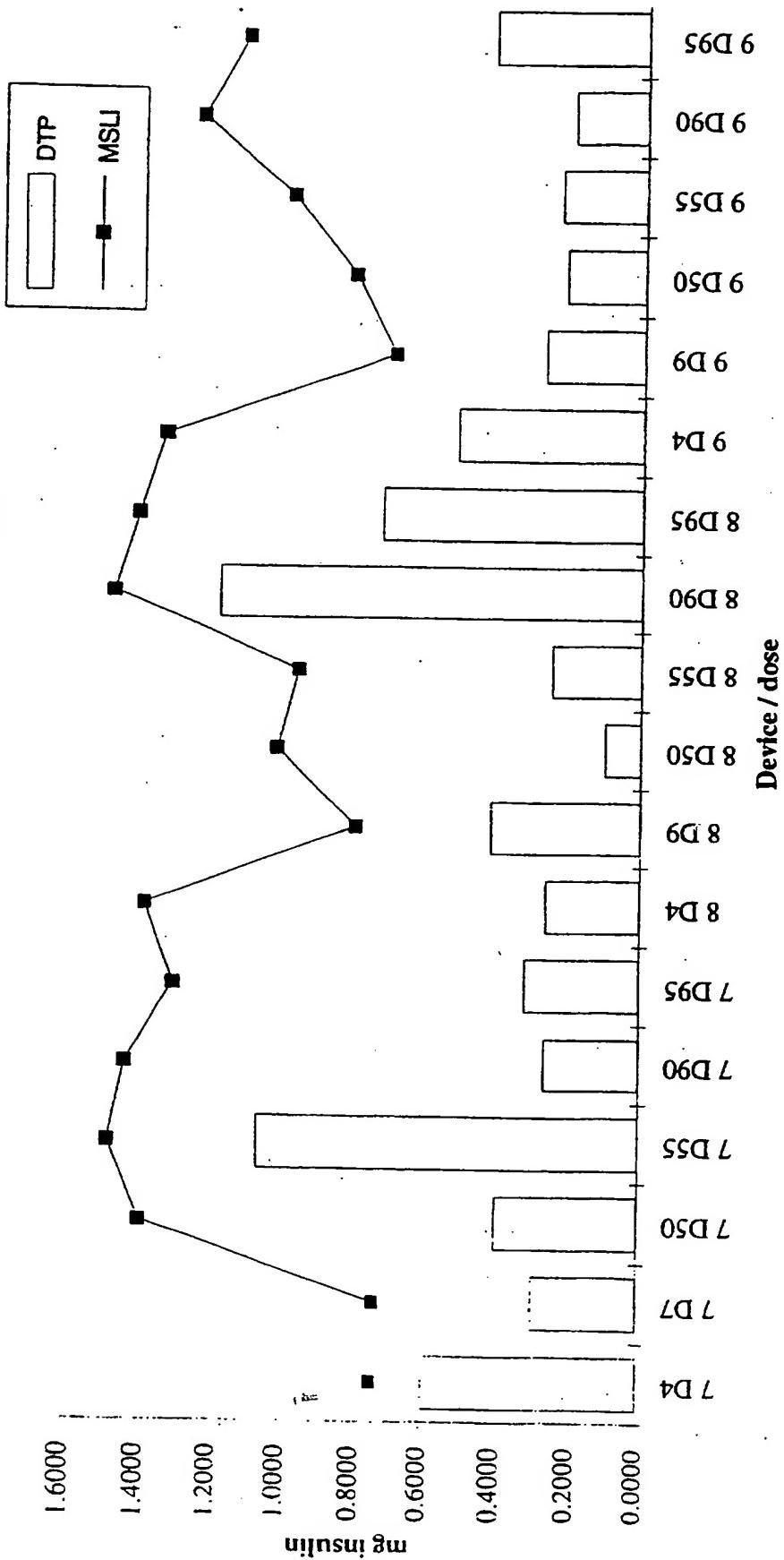
19. A composition as described in any one of Claims 1 to 18 wherein the particles provide an immediate release of the pharmacological agent once deposited in the lungs.
- 5 20. A composition as described in any one of Claims 1 to 18 wherein the addition of a crosslinking agent or other excipients provides a controlled release of the pharmacological agent once deposited in the lungs.
- 10 21. A method for the improved systemic delivery of pharmacological agents to a mammal by the respiratory tract wherein the agent is incorporated into a polysaccharide microparticle through a process of spray drying.
- 15 22. A method for the improved systemic delivery of pharmacological agents to a mammal by the respiratory tract which comprises administering a composition according to any one of Claims 1 to 20 to a patient.
- 20 23. A method as described in Claim 21 or Claim 22 wherein the microparticle is administered using a dry powder device.
24. The use of a composition according to any one of Claims 1 to 20 in the manufacture of a medicament for use in the improved systemic delivery of pharmacological agents to a mammal by the respiratory tract.
- 25 25. A composition according to any one of Claims 1 to 20 for use in the improved systemic delivery of pharmacological agents to a mammal by the respiratory tract.
26. A method for preparing microspheres for the improved delivery of pharmacological agents to the respiratory tract of a mammal wherein the said agent is incorporated into a microsphere using a one step process where the

drug is mixed in solution with a soluble polysaccharide and thereafter particles formed through a process of spray drying.

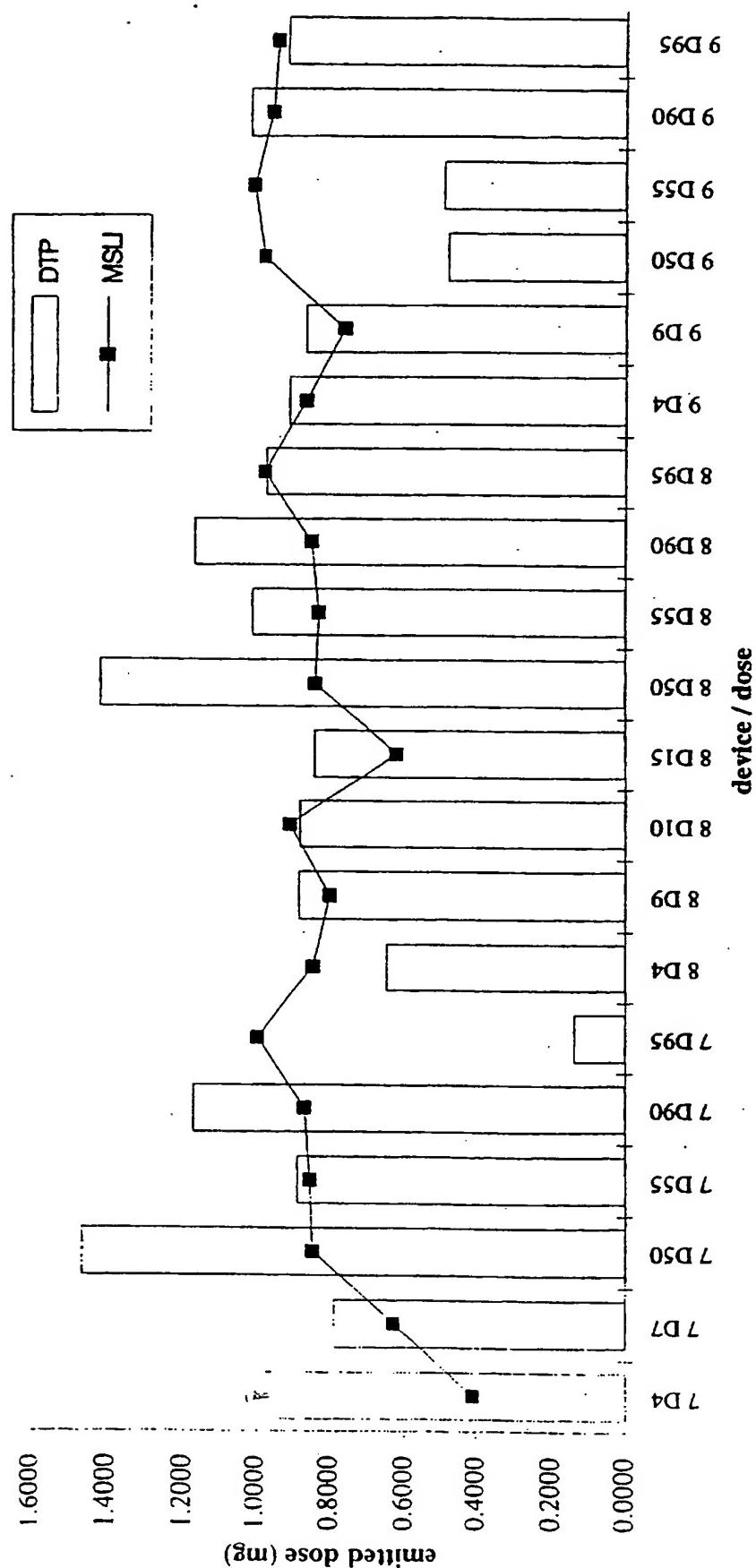
27. A microsphere obtainable by the method of Claim 26.

1/2

Figure 1 Emitted dose - micronised insulin



2/2

**Figure 2** Emitted dose - insulin microspheres

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 97/00808

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 A61K9/16	A61K9/00	A61K38/28	A61K38/23	A61K31/135
A61K31/485	A61K38/27	A61K9/50		

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 96 03978 A (QUADRANT HOLDINGS CAMBRIDGE LTD) 15 February 1996</p> <p>see page 17, lines 22-28; page 18, lines 12-14; page 30, line 3 - page 31, line 27; page 37, lines 17-28; page 38, lines 1-19; page 42, lines 24-29; page 45, lines 12-19; page 46, lines 10-18; claims 1, 2, 4, 6, 14, 15, 18, 19, 21-25, 38, 43, 46</p> <p>---</p>	<p>1-5, 7, 11, 12, 15, 18, 21-27</p>
A	<p>WO 93 15737 A (DANBIOSYST UK LTD) 19 August 1993</p> <p>see the whole document</p> <p>---</p> <p>-/-</p>	<p>1, 8, 10-12, 15, 17-20</p>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*&\* document member of the same patent family

Date of the actual completion of the international search

25 August 1997

Date of mailing of the international search report

08.09.97

Name and mailing address of the ISA

European Patent Office, P.B. 3818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Van Amsterdam, L

## INTERNATIONAL SEARCH REPORT

Int'l. Jpnal Application No  
PCT/GB 97/00808

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 611 567 A (TEIJIN LTD) 24 August 1994 cited in the application see page 7, line 10 - page 8, line 34; examples; claims ---	1-5,18, 21-27
P,X	WO 96 09814 A (ANDARIS LTD) 4 April 1996  see page 5, lines 25 - 35; page 9, lines 19-26; page 12, line 29 - page 13, line 9; claims 1-7, 10, 16-19 -----	1-5,8, 11,18, 21-27

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 97/00808

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 21-23 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No

PCT/GB 97/00808

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9603978 A	15-02-96	AU 3185195 A CA 2197982 A EP 0773781 A FI 970867 A NO 971688 A NZ 290896 A PL 318898 A		04-03-96 15-02-96 21-05-97 08-04-97 11-04-97 24-04-97 21-07-97
-----				
WO 9315737 A	19-08-93	AU 3458093 A EP 0625044 A GB 2277682 A,B JP 7503481 T NO 942787 A US 5629011 A		03-09-93 23-11-94 09-11-94 13-04-95 27-07-94 13-05-97
-----				
EP 611567 A	24-08-94	AU 659328 B AU 4355693 A AU 660824 B AU 4355593 A CA 2115065 A CA 2115444 A EP 0606486 A WO 9325193 A WO 9325198 A US 5626871 A		11-05-95 04-01-94 06-07-95 04-01-94 23-12-93 23-12-93 20-07-94 23-12-93 23-12-93 06-05-97
-----				
WO 9609814 A	04-04-96	AU 3530295 A CA 2199954 A EP 0783298 A FI 971332 A NO 971438 A		19-04-96 04-04-96 16-07-97 01-04-97 26-03-97
-----				

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

**BLACK BORDERS**

**IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

**FADED TEXT OR DRAWING**

**BLURRED OR ILLEGIBLE TEXT OR DRAWING**

**SKEWED/SLANTED IMAGES**

**COLOR OR BLACK AND WHITE PHOTOGRAPHS**

**GRAY SCALE DOCUMENTS**

**LINES OR MARKS ON ORIGINAL DOCUMENT**

**REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

**OTHER:** \_\_\_\_\_

## **IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**